Example 4

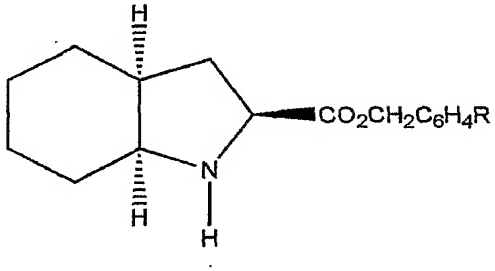
Preparation of Perindopril erbumine

The oil obtained from Example 3 (24 gm) was dissolved in dichloromethane (230 ml) and cooled below 10°C. 1-hydroxybenzotriazole (6 gm) and N-[(S)-1-carbethoxybutyl]-(S)-alanine (21.26 gm) were added to the reaction mass. The solution of DCC (25 gm) in MDC (100 ml) was added drop wise to the reaction mass below 15°C in about 60 min. The reaction mass was stirred for 4 hrs at 10-15°C and was filtered through celite. The filtrate was then washed with saturated solution of sodium bicarbonate followed by water. Dichloromethane was concentrated at 50°C under vacuum to get oil which was dissolved in diisopropyl ether and chilled to 10°C, stirred for 30 min and filtered through celite. The filtrate was then concentrated to get a yellowish oil (43 gm).

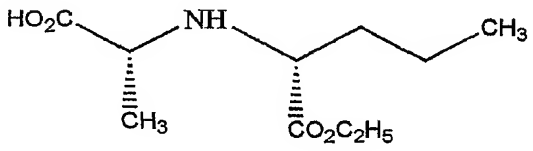
The oil was dissolved in isopropyl alcohol (430 ml). Tert-butyl amine (20.5 gm) was added and hydrogenated at 40 psi for 3 hrs using 10% Pd/C (50% wet, 7 gm). After completion of reaction catalyst was filtered through celite and the filtrate was vacuum distilled below 40°C. Traces of isopropyl alcohol were removed by co-distilling with acetone (400 ml) under vacuum. Acetone (100 ml) was added, warmed up to 45-50°C, and stirred for 30 min. It was then cooled to 10-15°C, filtered and washed with acetone. After drying at 40°C, perindopril erbumine (20.5 gm) was obtained as white crystalline solid.

CLAIMS

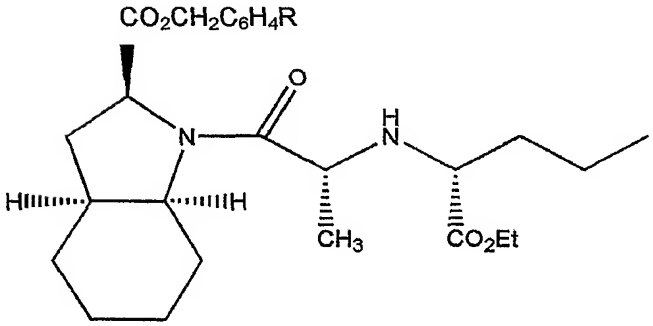
1 A process for preparing perindopril, or a pharmaceutically acceptable salt thereof, which process comprises coupling a substituted benzyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (I) with N-[(S)-carbethoxybutyl]-(S)-alanine (II):



I



II



III

where R represents a halo, C_{1-4}alkoxy or nitro substituent, to form the ester of formula III, wherein the coupling is carried out in the presence of N,N-dicyclohexyl carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT): and converting the ester of formula III to perindopril or a pharmaceutically acceptable salt thereof.

2 A process according to claim 1, wherein R represents a 4-substituent.

3 A process according to claim 1 or 2, wherein the coupling is carried out at a temperature below 20°C, preferably in the range 10-15°C.

4 A process according to claim 1, 2 or 3, wherein from 1.5 to 1.7 mole DCC are employed per mole of the ester of formula I.

5 A process according to any of claims 1 to 4, which includes deprotection the compound of formula III by hydrogenolysis in the presence of a noble metal catalyst.

6 A process according to claim 5, wherein the catalyst is palladium on carbon.

7 A process according to any of claims 1 to 6 wherein the perindopril is converted to a pharmaceutically acceptable salt.

8 A process according to claim 7, wherein the perindopril is converted to the tert butyl amine salt.

9 A process for preparing perindopril, or a pharmaceutically acceptable salt thereof, which includes an intermediate process step wherein an aralkyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid is prepared by reaction of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid with an aralkyl alcohol, wherein either said (2S,3aS,7aS)-octahydroindole-2-carboxylic acid is treated with an excess of the alcohol and thionyl chloride, excess alcohol is distilled off and the residue treated with a solvent to obtain the aralykyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid as a hydrochloride; or said (2S,3aS,7aS)-octahydroindole-2-carboxylic acid is treated with an excess of the alcohol and heated with toluene using a molar quantity p-toluene sulphonic acid, to obtain the aralkyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid as a salt, and converting the salt to the base, preferably by treatment with ammonia.

10 A process according to claim 9, wherein the aralkyl alcohol has a substituent in the aryl group.

11 A process according to claim 10, wherein the aryl group has a halo, alkoxy or nitro substituent.

12 A process according to claim 11, wherein the aryl group has a 4-chloro, 4 C_{1-4}-alkoxy or 4-nitro group, substituent.

13 A process according to any of claims 9 to 12, wherein the aralkyl group is a benzyl group or a substituted benzyl group.

14 A process according to any of claims 1 to 8, wherein the compound of formula I has been made a process according to any of claims 9 to 13.

15 A process for preparing perindopril, or a pharmaceutically acceptable salt thereof, which includes an intermediate process step which comprises conversion of an alkali metal salt of S-indoline-2-carboxylic acid to (2S,3aS,7aS)-octahydroindole-2-carboxylic acid by hydrogenation at a pressure of from 5 to 20 bar.

16 A process according to claim 15, wherein the hydrogenation is carried out at a pressure of 10 to 15 bar.

17 A process according to claim 15 or 16, wherein said hydrogenation is effected in the presence of alkali and the octahydroindole-2-carboxylic acid salt so formed is treated with mineral acid to release the free acid.

18 A process according to any of claims 15 to 17, wherein the alkali metal salt of said S-indoline-2-carboxylic acid is the sodium salt.

19 A process according to any of claims 15 to 18, wherein the hydrogenation is carried out in a polar solvent selected from C_{1-4} alcohols and water, or mixtures thereof.

20 A process according to any of claims 15 to 19, wherein the product is crystallized from acetonitrile.

21 A process according to any of claims 15 to 20, wherein said catalyst is 5% rhodium on alumina.

22 A process according to any of claims 9 to 14, wherein the (2S,3aS,7aS)-octahydroindole-2-carboxylic acid has been made by the process of any of claims 15 to 21.

23 A process for preparing perindopril, or a pharmaceutically acceptable salt thereof, which includes an intermediate process step which comprises condensation of norvaline ethyl ester with pyruvic acid to yield N-[(S)-1-carbethoxybutyl]-(S)-alanine (II), wherein said condensation is carried out under catalytic hydrogenation and said catalyst and any inorganic salts present in the reaction medium are removed by filtration to obtain a filtrate, the filtrate is concentrated and N-[(S)-1-carbethoxybutyl]-(S)-alanine is isolated by precipitation by the addition of a solvent selected from acetone, acetonitrile and ethyl acetate.

24 A process according to claim 23, wherein the condensation is effected in a lower alcohol, preferably ethanol.

25 A process according to claim 23 or 24, wherein said norvaline ethyl ester is included in the reaction medium as the hydrochloride salt thereof, in the presence of a base.

26 A process according to claim 23, 24 or 25, wherein said catalytic hydrogenation is carried out in a hydrogenator, in the presence of palladium on carbon as the catalyst.

27 A process according to claim 26, wherein said catalyst is 10% palladium on carbon.

28 A process according to any of claims 23 to 27, wherein said hydrogenation is carried out at a pressure in the range of 5 to 10 bar.

29 A process according to any of claims 23 to 28, wherein the precipitation solvent for N-[(S)-1-carbethoxybutyl]-(S)-alanine is acetone.

30 A process according to any of claims 1 to 14 and 22, wherein compound II has been made by the process of any of claims 23 to 29.

31 A process according to any of claims 9 to 30, which further comprises converting perindopril free base to perindopril erbumine.

32 Perindopril, or a pharmaceutically acceptable salt thereof, prepared by a process according to any of claims 1 to 31.

33 A pharmaceutical composition comprising an effective ACE inhibitory amount of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 32, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

34 Use of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 32, in the manufacture of a medicament for inhibiting ACE.

35 A method of inhibiting ACE in a patient in need thereof, comprising administering to said patient an effective ACE inhibitory amount of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 32.